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Advances In Cancer Immunotherapy

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ABSTRACT

Immunotherapy has transformed cancer treatment by harnessing a patient's own immune system to fight against their own malignant cells. Replacing chemotherapy and radiation strategies to directly target the tumor, immunotherapy using neoantigens creates a stronger and more enduring response. This review examines the three most common immunotherapies: Chimeric Antigen Receptor T cell therapy, Tumor Infiltrating Lymphocyte therapy, and Hematopoietic Stem Cell Transplantation, analyzing the process, results, effectiveness, disadvantages, and future applications. A literature review of FDA approvals, historical studies, and advancements was used to evaluate each therapy. Advancing from T-cell therapy, CAR T cell therapy has shown strong response rates of 68–90% in pediatric B-cell cancers and strong remissions, but it presents risks such as cytokine release syndrome, B cell aplasia, and neurotoxicity. While only applied to metastatic myeloma, TIL therapy shows response rates of 34–72% , though its complexity, toxicity, and cost are current limitations of this therapy. HCT, mainly used for hematologic cancers like acute myeloid leukemia, has prominent response rates of 45–60%, but difficulty in finding a donor and graft-vs-host disease remain challenging. Findings show that immunotherapies have the potential to be very effective cancer treatment strategies.

Keywords:

Cancer immunotherapy, Chimeric Antigen Receptor T-cell therapy (CAR T-cell therapy), Tumor-infiltrating lymphocyte therapy (TIL therapy), Hematopoietic Stem Cell Transplantation (HCT), Adoptive T-cell transfer, Neoantigens. Response rates, cytokine release syndrome, graft-versus-host disease, melanoma. Leukemia; Lymphoma

INTRODUCTION

In recent years, immunotherapy has transformed the medical field and treatment for diseases, especially cancer. It consists of taking advantage of the body's own immune system to combat diseases. Cancer is defined as the uncontrolled cell growth that commonly spreads around the body, causing damage. Unlike original cancer treatments, which eliminate cancer cells directly, immunotherapy makes the immune system target cancer markers, or neoantigens. Three of the most promising and established immunotherapies include chimeric antigen receptor (CAR T) cell therapy, where cells are removed, modified, and reintroduced; tumor-infiltrating lymphocyte (TIL) therapy, where specific cells are

removed, multiplied, and placed back in the tumor; and hematopoietic stem cell transplantation (HCT) therapy, where healthy stem cells are infused into the patient's body. These treatments use different techniques to target multiple cancers and differ significantly. The goal of this review is to provide a tool to summarize each treatment by analyzing the treatment's process, the cancer it targets, and the benefits and costs associated. Finally, it also intends to provide insights into the future of cancer research.

CAR-T CELL THERAPY

In the 1980s, initial immunotherapy research started from adoptive T-cell transfer research. Adoptive T-cell therapy consists of cells that are reinfused into patients' bodies after being genetically modified by inserting special receptors on their surface to fight specific cancers. Initial efforts were focused on CAR T therapies. Domains, which are parts of proteins crucial for treatment, allow T cells to identify cancer cells and subsequently activate a response to kill them. The first generation of CAR T cell therapies only contained one signaling domain

CD3ζ, which lacked persistence and did not last long enough to sustain an anti-tumor response. The major breakthrough of CAR T cells happened when the second generation was created with co-stimulatory domains such as CD28 and CD137. Co-stimulatory domains let CAR T cell therapies last longer and be more effective. CAR T cell therapies were successfully tested with B cell cancers, or blood cancers, because the therapy targets the CD19 protein presented on the B cell, along with B cells circulating in the blood system, making them accessible. In 2017 the therapy got FDA approval for leukemia. CAR T cells are made by collecting a patient's T lymphocytes, or white blood cells, and modifying them ex vivo—the process of changing cells outside the body in a lab—to express a chimeric antigen receptor, which recognizes the antigen of the cancer cells. The CAR structure is made up of four parts. It includes an scFv—a single-chain variable fragment—that targets the tumor antigens such as CD19; a transmembrane domain linking the receptor to the cell membrane; the CD3ζ domain, providing the first signal to attack; and finally, the co-stimulatory domain, like CD28 and CD137, for the second signal. The cells are then infused back into the body through blood transfusion and actively attack cancer cells by identifying the target antigen. The way immunotherapies are evaluated is by their response rates to certain cancers, which show the therapies' strengths and what they should be used for. Response rates show the percentage of cancer patients whose tumors or cancer shrinks. CAR-T cell therapy has a 68-90% response rate for pediatric B-cell cancer (C. H. June, M. Sadelain. Chimeric antigen receptor therapy. *N Engl J Med*. **379**, 68 (2018)), meaning that most children have successful remission with leukemia treatment with CAR-T. For diffuse large B-cell lymphoma, the response rate is 64%-86%, along with 40%-50% obtaining complete remission (C. H. June, M. Sadelain. Chimeric antigen receptor therapy. *N Engl J Med*. **379**, 68 (2018)). Overall, CAR T cells show high response rates and durable remissions for blood cancers and offer targeted specialties by focusing on specific antigens like CD19. This shows one of CAR-T's many benefits. In addition, CAR-T cells have long-term immune memory that can

persist for years while also multiplying in the patient's body and avoiding multiple treatments. While there are many benefits, there are also drawbacks. CAR-T cell therapy can cause many side effects, like cytokine release syndrome triggered by T cell activation releasing too many inflammatory molecules or cytokines. This generates high fevers, low blood pressure, and organ stress. The brain and nervous system can also be affected, and neurotoxicity can cause confusion, seizures, and headaches. Finally, patients can also experience B-cell aplasia because CAR-T cells can sometimes also attack healthy B cells. In the future CAR-T cells may target multiple antigens, with the possibility of CAR-T cells being allogenic and received from healthy donors with CAR-T cells. Overall, CAR-T cell therapies are very powerful and continue to evolve to be a stronger and more versatile solution for cancer treatment.

TUMOR-INFILTRATING LYMPHOCYTE THERAPY

Tumor-infiltrating lymphocyte (TIL) therapy was first invented in the late 1980s by Rosenberg and collaborators at the National Institute of Health. TIL therapy is a type of immunotherapy where the patient's immune cells, which successfully recognize the cancer, are taken out of the body, grown in large numbers in a lab, and infused back into the patient's body. TIL emerged from a broader field of adoptive cell transfer, which is isolating and expanding a patient's immune cells to fight cancer. Initial studies in metastatic melanoma were promising but lacked durability. Eventually refinements such as optimized lymphodepleting chemotherapy, which eliminates the patient's original immune cells, and IL-2, which signals TIL growth, improved the therapy. Recently TIL has been FDA-approved for metastatic melanoma. There are many steps during the process of TIL therapy. First, the patient's tumor is surgically removed, and tissue is cultured in IL-2 to multiply the naturally occurring successful lymphocytes. For 14 days they are cultured and massively expanded using a high dose of IL-2, anti-CD3 antibodies that mimic a strong activation signal, and irradiated feeder cells that prevent division and support growth by providing signals and nutrients. The patient then goes through lymphodepleting chemotherapy, which suppresses their immune system and makes space for TILs. Finally, the expanded TILs are infused back into the patient along with the dose of IL-2 to support T-cell survival. Metastatic melanoma has response rates of 34%-72%, and uveal melanoma has a response rate of 35% ((A. S. Hinrichs, S. A. Rosenberg. Adoptive cell therapy for cancer: TILs and beyond. *J Clin Oncol*. **32**, *3276* (2014).)). This shows that TIL shows consistent response rates in solid tumors, especially in melanoma, or skin cancer. Over time, rates have improved through refinements of IL-2 and lymphodepletion. TIL is very successful because of its many advantages. For example, TIL is personalized, so it reduces antigen escape, ensuring that the cancer cells do not stop expressing the target antigen. In addition, TIL has very durable responses and utilizes natural tumor reactivity. While it has many strengths, it also has downsides such as toxicity because of the lymphodepleting chemotherapy and high doses of IL-2. It is also limited because it is resource-intensive, expensive, and complex. Finally, while it has the potential to expand as a treatment for other cancers, it is currently limited to melanoma. In the future, neoantigen-specific TILs, which are TILs that only target neoantigens, could be used. This is relevant because it limits the number of healthy cells that are affected, given that only cancerous cells have neoantigens. Additionally, there could be genetically modified TILs,

which can be enhanced by inserting different receptors and can also expand the number of tumors that TILs can target.

Despite current limitations, TIL therapy is the most effective treatment against tumors and melanoma ((A. S. Hinrichs, S. A. Rosenberg. Adoptive cell therapy for cancer: TILs and beyond. *J Clin Oncol*. **32**, 3275 (2014).)), and it has the potential to be a more effective and safer treatment for other tumorous cancers.

HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic Cell Transplantation (HCT) first began in the 1950s to restore bone marrow function. The therapy was soon tested in humans in 1957 when Thomas ED infused donor marrow into leukemia patients. Initial applications of this therapy were complicated due to graft rejection and graft-host diseases and led to poor outcomes where 200+ people died (N. Granot, R. Storb. History of hematopoietic cell transplantation: Challenges and progress). *Haematologica*.**105**, 2716 (2020)). During the 1960s and '70s the field gained traction with better outcomes in leukemia and aplastic anemia. Today, more than 1.5 million hematopoietic stem cell transplants have been performed (N. Granot, R.

Storb. History of hematopoietic cell transplantation: Challenges and progress. *Haematologica*. **105**,

2716 (2020)). HCT is a procedure where a patient's damaged bone marrow is replaced by hematopoietic or blood-forming stem cells. These stem cells can come from a healthy matched donor or from a non-matched donor. Donors can be unrelated or siblings as long as their human leukocyte antigens match, or the proteins on the surface of their cells or major histocompatibility complex (MHC) match. When there is a donor that does not match the MHC or the protein on the cell surface, the chance of complications increases. Before cells are infused, there has to be enough space for donor cells, and this space is made through chemotherapy. There are two different types of chemotherapy regimens, including myeloablative, which is a high-dose chemotherapy that destroys diseased marrow, and reduced-intensity, which is chemotherapy in lower doses for older or extremely fragile people. Stem cells from the donor’s bone marrow, blood stem cells, or umbilical cord blood are infused into the patient’s bone marrow through intravenous application. The new cells engraft the bone marrow and repopulate the immune system. HCT is most effective for blood-related diseases such as acute myeloid leukemia (AML). AML has a 45%-60% five-year survival (N. Granot, R. Storb. History of hematopoietic cell transplantation: Challenges and progress. *Haematologica*. **105**, 2719 (2020), which is positive for how aggressive the cancer is. HCT is used best during early transplants and low disease burden, meaning when a small amount of cancer is left in the body. HCT is great for many malignant and nonmalignant diseases and reduces relapse in leukemia and lymphoma. It also is very versatile with flexible donor options and is successful in young and old patients. Although it has multiple benefits, there are some extreme problems with this treatment. The worst one is graft-versus-host disease, which

is when the donor cells attack the patient's healthy cells because they recognize them as foreign and mount an immune response. In addition, there can be toxicities, relapse, and even infections. Finally, it can be hard for people to find donors, making the whole process difficult. Future advancements that can be made is selective T-cell depletion to prevent graft versus host disease, along with vaccines and alpha-emitting radioimmunotherapy, which can target tumors.
cells with minimal toxicity in the immune system. Despite its challenges, hematopoietic stem cell transplants are a staple therapy for many hematologic diseases and have ongoing advances.

Discussion:

In comparison to chemotherapy, CAR-T therapy, TIL therapy, and hematopoietic stem cell transplants all show higher remission rates. In addition, they are all specific to attacking cancer antigens and do not kill all rapidly dividing cells like chemotherapy. They also have very different versions of relapse; for chemotherapy it is due to unsuccessful targeting of the antigens, while in immunotherapy it is due to the cancer itself evolving and escaping the therapy. While the new emerging therapies are overall better than chemotherapy, they are also all different from each other. For cost and accessibility, HCT is widely used compared to TIL, which is time-intensive, and CAR-T, which is limited. Clinically, HCT is the most commonly used, TIL is very rare (limited to melanoma), and CAR-T is increasing rapidly, especially for B-cell cancer. While different, they are similar in the fact that they are all currently expensive and have limited access.

THE FUTURE OF IMMUNOTHERAPY

While CAR T therapy, TIL therapy, and hematopoietic stem cell transplants have been huge advancements in the field of immunotherapy, they are not always completely successful, as the immune system does not always fully eliminate cancer because many tumors adapt and survive. The reason that these three therapies are not ideal is because of the idea of "elimination," "equilibrium," and "escape." (Smyth, M. J., Dunn, G. P., Schreiber, R. D. Cancer immunoediting: Integrating immunity's roles in cancer suppression and promotion. *Science*. **331**, 1565–1570 (2011). Elimination is where the immune system is winning; it is when the immune system finds the cancer cells and T cells attack and destroy them, which is good. Equilibrium is when they are tied; some cancer cells survive, but the immune system keeps them under control. Finally, escape is when the cancers escape the immune system; they evolve and become stronger. They find ways to hide from T cells, suppress the immune system, and stop showing antigens. This leads to resistance to the therapies along with relapse of cancer. There are now new emerging therapies that help prevent equilibrium and escape, starting with the new additions to CAR-T therapies. Scientists have now started to use CRISPR—a type of gene editing—to change CAR-T cells. The new CRISPR technology removes the PD-1 gene (S. R. Eyquem et al. Targeting a CAR to the TRAC locus with CRISPR/Cas9 enhances tumor rejection). Nature. **543**, 113 (2017)), which makes the T cells stay active longer and makes them stronger. This fixes one of CAR-T cells' biggest problems, which is the cells stopping too early. In addition, there is the new dual-target CAR-T cell, which targets two

antigens: CD19 and CD22 (Q. Liu et al. Dual targeting of CD19 and CD22 against B-cell malignancies using CAR-T cells. Nat Med. **25**, 623 (2019)). This is an important step in preventing escape since the cancer has to lose both antigens, which is significantly harder than just losing one. Finally NK cell therapy, which replaces T cells with natural killer (NK) cells. They automatically kill abnormal cells and do not need exact antigen matching. (X. Liu et al. Chimeric antigen receptor natural killer (CAR-NK) cells for cancer immunotherapy. Nat Rev Clin Oncol. **17**, 147 (2020)). This drug can be made from donors, stored on the shelf, and has way fewer side effects. This is very beneficial because it is faster and cheaper than all the other therapies mentioned and, hence, a lot more accessible. While these treatments are not FDA-approved yet and are still being experimented with, they offer an insight into the future of cancer immunotherapy with their ability to overcome immune escape and reduce toxicity. They show how the study of immunotherapy is constantly evolving and improving.

CONCLUSION

In conclusion, CAR T-cell therapy, TIL therapy, and HCT therapy are the three most modernized treatments in the field of cancer immunology. While each one uses the immune system in a different way, they each have their own specific pathways to treat and eliminate cancer. CAR T-cell therapies are best for blood cancers, while TIL works well in melanoma and HCT in different blood-related cancers. While each treatment has negative effects and disadvantages, their clear benefits highlight why they are so important and how they are changing the future of medicine.

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